Prostate Cancer: Risk Assessment and Diagnostic Approaches

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The successful treatment of prostate cancer relies on detection of the disease at its earliest stages. Although prostate-specific antigen (PSA)-based screening has been a significant advance in the early diagnosis of prostate cancer, identifying specific genetic alterations in a given family or patient will allow more appropriate screening for early disease. Mapping and identification of specific prostate cancer susceptibility genes is slowly becoming a reality. Other prostate cancer risks include a family history, race, and possibly serum markers such as insulin-like growth factor-I (IGF-I). Once a high-risk man is identified, transrectal ultrasound (TRUS)-guided biopsies are the standard to diagnose prostate cancer. Although TRUS is an advance over traditional digitally directed biopsies, it represents a random sampling of the prostate since most lesions cannot be visualized. Newer modalities such as ultrasound contrast agents, pattern recognition, and artificial neural networks (ANNs), applied to TRUS images, may improve diagnostic accuracy. If a man at risk for prostate cancer has undergone a negative TRUS biopsy, the decision for the need for additional biopsies is problematic. Use of PSA derivatives such as free and total PSA and the initial biopsy abnormalities such as atypia or high-grade prostatic intraepithelial neoplasia may define those patients in need of follow-up biopsy.
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Improvements in screening and diagnosing prostate cancer have occurred with the use of prostate-specific antigen (PSA) and the development of gray-scale transrectal ultrasound (TRUS) biopsy techniques. As the human genome project moves forward, we may be able to identify specific abnormalities that may predispose to cancer and thus alter our screening approach. Likewise, new markers, exemplified by serum insulin-like growth factor-I (IGF-I), may predict future development of the disease. Enhancements in TRUS biopsy, including contrast agents, artificial neural networks, and the parameters for follow-up biopsy will improve the accuracy of our current diagnostic techniques. This report presents highlights of papers presented at

Table 1
Potential Genetic Alterations Under Study in Prostate Cancer

- *HPC1* at 1q24
- *PCAP* at 1q42
- *HPCX* at Xq27
- *HPC20* at 20q13.18
- *CAPB* at 1p36
- *ELAC2* at 17p12
- *BRCA1/BRCA2*
- 5α-reductase type II gene (*SRD5A2*) at 2p23-22
- Androgen receptor alterations (CAG, CCG repeats)

the 11th International Prostate Cancer Update held in Vail, Colorado that addressed these current issues in the early diagnosis of prostate cancer.

Prostate Cancer Susceptibility Genes

The prevalence of prostate cancer varies markedly between different ethnic groups, with the highest frequency in African Americans and the lowest frequency in Asian populations. This ethnic disparity may be attributable to environmental factors, genetic factors, or both. Studies have investigated the role of family history as a risk factor for prostate cancer.[1,2] Reports of families with large numbers of cases, as in the Utah Mormon population, have been key for exploring inherited prostate cancer.[3,4] The risk of prostate cancer increases with younger age of onset in a relative or when the number of affected individuals in a familial cluster increases. This increased risk is strong evidence for a genetic component. For example, the brother of a man diagnosed at age 50 has a relative risk of 1.9 times of developing a prostate cancer compared with a brother of a case diagnosed at age 70.[5] Having two or three first-degree relatives affected increases the relative risk by 4.9 and 10.9 times, respectively.[6] Monozygotic twins have a fourfold increased rate of prostate cancer compared with dizygotic twins.[7] Estimates using the combined data from 44,788 sets of twins in Swedish, Danish, and Finnish registries suggest that up to 42% of all prostate cancer risk may be explained by inheritable factors.[5] Identification of these specific genetic alterations that place a man at a higher risk of developing and dying of prostate cancer is an area of intense investigation that is further facilitated by the Human Genome Project. A list of potential genetic alterations in prostate cancer can be found in Table 1.

A correlation between CAG repeat length in the androgen receptor and age of onset of prostate cancer has been observed.[8] A study of 587 individuals demonstrated an inverse relationship between CAG repeat length in the androgen receptor (AR) gene and risk of aggressive prostate cancer.[9] Other studies support an association between reduced AR CAG repeat length and increased risk of prostate cancer, the length of the polymorphism GGC repeat in the AR being an additional potential risk factor.[10]

Four prostate cancer susceptibility loci (*HPC1* at 1q24, *PCAP* at 1q42, *HPCX* at Xq27, and *CAPB* at 1p36) have been described and tested on independent data sets.[11-14] Another recent study presents significant evidence for linkage to a new locus, *HPC20* at 20q13.[15] Of these, only the *HPC1* linkage has a reasonable level of independent confirmation; other studies found no significant evidence for linkage.[3,16,17] Although the initial report of linkage to *HPC1* suggested that up to 34% of prostate cancer families could be related to this locus, a subsequent pooled analysis of 772 families demonstrated the proportion to be about 6%.[18]

Positional cloning techniques have identified *ELAC2*, a candidate prostate cancer susceptibility gene at 17p12.[19] This is the first prostate cancer susceptibility gene cloned after a genome-wide scan of high-risk families. There is evidence that both frameshift and missense mutations are disease associated at this locus.

Familial co-segregation of breast and prostate cancer has also been reported. In breast/ovarian cancer families, male carriers of a deleterious mutation in *BRCA1* or *BRCA2* have been shown to be at a three- and sevenfold risk of prostate cancer, respectively.[20,21]

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Prostate cancer is the cancer most sensitive to hormonal manipulation. Analyses of genes encoding proteins involved in androgen biosynthesis and action led to the observation of a significant association between common genetic variants and a susceptibility to prostate cancer. One such gene is the 5α-reductase type II gene (*SRD5A2*), which catalyzes the conversion of testosterone into dihy-

Table 2
Published Studies on the Role of Elevated IGF-I and Prostate Cancer Risk

Study	Total no. in Study (Prostate Cancer/Control)	
Studies supporting an association		
Chan et al, 1998[29]	304	(152/152)
Montzaros et al, 1997[28]	104	(52/52)
Wolk et al, 1998[27]	434	(210/224)
Studies not supporting an association		
Kanety et al, 1992[30]	34	(24/10)
Cohen et al, 1992[31]	48	(32/16)
Ho et al, 1997[32]	31	(16/15)
Schaefer and Friedman, 1998[33]	215	(45/170)
Baffa et al, 2000[36]	96	(57/39)
Shariat et al, 2000[35]	150	(120/30)

drotestosterone (DHT) and maps to 2p23-22.[22]

The growing body of knowledge of the potential familial aspects of prostate cancer provides an important tool for understanding the mechanisms underlying the molecular basis of prostate cancer. Study of the genetic aspects of tumor initiation and progression will probably yield more effective screening, treatment, and prevention strategies in the future.

IGF-I as A Marker for Prostate Cancer

The IGF system consists of a series of ligands (IGF-I, IGF-2, insulin), binding proteins (IGF binding proteins 1–6), and receptors. IGF-IR (also known as the type I IGF receptor) binds both IGF-I and IGF-II and is a cell surface receptor in the tyrosine kinase class. The IGF-II receptor preferentially binds IGF-II but does not appear to transduce a mitogenic signal. IGF-I has been proved to be an important mitogenic and antiapoptotic peptide in many tumors, including breast, lung, and colorectal, as well as prostate cancer.[23,24] In vitro studies have established that human prostate cancer cell lines have functional IGF-I, with blockage of the receptor leading to cessation of growth.[25,26] The presence of IGF-I in prostate cells and its potential role in the growth and development of cancer suggest that IGF-I may serve as a predictor of prostate cancer or potential target for prostate cancer therapy.

The prostate cancer literature presents conflicting evidence to the predictive value of IGF-I and the development of prostate cancer. Some studies show a positive relationship between IGF-I and prostate cancer, whereas others show an inverse relationship or no relationship at all (Table 2).

An association between elevated levels of plasma IGF-I and an increased risk of prostate cancer has been shown in a number of studies. There appears to be no correlation between IGF-I and benign prostatic hyperplasia (BPH), but increased levels of IGF-I (> 60 ng/mL), are suggested to be associated with an increased risk of prostate cancer. Three studies (by Wolk et al,[27] Montzaros et al,[28] and Chan et al[29]) support a statistically significant association between elevated IGF-I levels and the risk of developing prostate cancer.

Other studies do not come to the same conclusion. These studies have compared prostate cancer patients with counterparts who have normal prostates and benign prostatic hypertrophy.[30–36] Several of these studies have actually suggested an inverse relation between IGF-I levels and risk.[33,36] In patients undergoing radical prostatectomy for localized disease, plasma IGF-I levels predicted neither organ-confined disease nor the risk of PSA progression and did not correlate with preoperative PSA level or final Gleason score.

There may be many reasons for these diverse observations: the specific IGF-I assay system used, treatment with hormonal therapy, and, most importantly, consideration of the effects of IGF binding proteins on serum IGF-I levels. The role of IGF-I as a risk factor for prostate cancer deserves continued study.

With inhibition of the IGF-IR pathway, normal cells appear to simply stop growing, but cancer cells appear to die rapidly through an apoptotic mechanism. Impairment of the IGF-IR function has dramatic effects on cancer cells growing in anchorage independence compared with cells growing in monolayer.[37] If IGF-I proves not to be a reliable marker for the disease, it may still have a role in therapy.

Contrast-Enhanced Prostate Biopsy

Years of experience have shown that TRUS-directed prostate biopsy, although very useful, has several limitations.[38,39] Prospective TRUS imaging data have demonstrated that conventional gray scale is slightly superior to random chance in prostate cancer detection.[40] The trend is to increase the number of biopsies

in order to compensate for the limitations of the imaging alone.[41] The traditional lesion-directed biopsy led to the development of the six-core, or sextant, biopsy technique. Today, at least eight to ten biopsies are recommended to sample the prostate gland more adequately. These additional biopsies tend to be laterally directed. Imaging of the prostate must be improved in order to enhance the detection of cancer.

Enhanced ultrasound techniques, such as color flow Doppler imaging (CDI) studies, have been investigated to improve the diagnostic ability of TRUS. Although studies suggest that CDI has potential prognostic significance, CDI can overlap with prostatitis and has low sensitivity in detection of tumor blood flow within prostate cancer. Alterations in the vascularity of prostate cancer have focused attention on ways to visualize characteristic vascular abnormalities, such as microbubble contrast agents. The use of intravenous microbubbles (average diameter 2 to 5 μm leads to marked enhancement of the signal-to-noise ratio and enhanced visualization on TRUS.[42] Several vascular ultrasound agents are being studied for their use in prostate imaging; most such agents have demonstrated enhancement on gray-scale imaging (Table 3).

Table 3
Some Vascular Ultrasound Contrast Agents Under Study in Imaging Prostate Cancer

- Echovist (Schering, Berlin, Germany)
- Levovist (Schering)
- EchoGen (Sonus Pharmaceuticals, Bothell, WA)
- Imagent US (Alliance Pharmaceutical, San Diego, CA)
- Definity (DuPont Pharmaceuticals, Billerica, MA)

None of the agents are currently approved by the U.S. Food and Drug Administration for use in the evaluation of prostate cancer.

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A study using EchoGen (Sonus Pharmaceuticals, Bothell, WA) consisted of 15 patients with a rising PSA; 14 of the 15 had a negative prior biopsy.[43] CDI TRUS was performed before and after EchoGen administration and correlated with sextant biopsies. Abnormal microvessel patterns were noted in eight patients; in two of these the lesions were malignant, one patient was diagnosed with prostatitis, and in two the lesions were benign. False-negative results were observed in three patients. Levovist (Schering AG, Berlin, Germany) was used in nine cases of prostatic cancer, with blood flow images enhanced in all cases.[44] In both studies, the authors concluded that contrast CDI is a promising technique that may allow for better imaging of blood flow and more accurate detection of early malignant lesions. Bogers et al[45] were the first to report the use of contrast-enhanced three-dimensional power Doppler angiography in the human prostate. With Levovist as a contrast agent, 18 patients with a suspicion of prostate cancer were evaluated; the study findings indicated that contrast-enhanced power Doppler and three-dimensional image reconstruction offers a useful imaging tool with good potential to improve prostate cancer detection in the future.

Adequate enhancement of ultrasound imaging using microbubble contrast agents is dependent on the ability of these agents to traverse the tumor neovascularity safely without being destroyed. Unfortunately, conventional ultrasound systems deliver power levels sufficient to destroy microbubbles. A potential solution to this problem is the use of intermittent imaging. Standard gray-scale ultrasound image is refreshed at 30 frames per second; thus the amount of contrast agent available for each frame is that which enters the imaging plane in 1/30th of a second. This short period is usually not sufficient for contrast agents to enter small-diameter vessels. With intermittent imaging, the ultrasound beam is turned off for longer periods between each frame, allowing more contrast material to enter the imaging plane during this interscan period. An initial experience at Thomas Jefferson University with 26 subjects indicated that intermittent imaging might enhance visualization of malignant neovascularity, with several patients demonstrating enhancement of tumor foci not detected by conventional gray-scale imaging or CDI.

The group from Thomas Jefferson University has reported using Imagent (Alliance Pharmaceutical Corp., San Diego, CA) as a prostate contrast agent.[46] Twenty-six subjects

with an elevated PSA and/or abnormal digital rectal examination (DRE) were studied. Continuous gray-scale, intermittent gray-scale, phase inversion gray-scale, and power Doppler sonography of the prostate were performed and correlated with sextant biopsy results. The study demonstrated significant visible enhancement ($P < .05$) after administration of Imagent.

In another study, 60 subjects were evaluated with conventional gray-scale, harmonic gray-scale, and power Doppler sonography.[47] The evaluation was repeated using IV Definity (DuPont Pharmaceuticals, Billerica, MA). Gray-scale imaging was performed in continuous mode and with intermittent imaging using interscan delay times of 0.5, 1.0, 2.0, and 5.0 seconds. Sextant biopsy sites were scored prospectively as benign or malignant on baseline imaging, and again during contrast-enhanced TRUS. Prostate cancer was present in 37 biopsy sites from 20 subjects. Baseline imaging demonstrated prostate cancer in 14 sites from 11 subjects. Contrast-enhanced TRUS demonstrated prostate cancer in 24 sites from 15 subjects. Each of the five subjects whose prostate cancer was missed had only a single positive biopsy score (Gleason score ≤ 6). The improvement in sensitivity from 38% at baseline to 65% with contrast was significant ($P < .004$). Using the contrast agent Definity along with TRUS improves sensitivity for detection of malignant foci within the prostate without substantial loss of specificity.

The currently available data suggest that ultrasound contrast agents may enhance our ability to identify specific foci of prostate cancer on TRUS. In particular, higher grade cancers may be more easily detected than low-grade lesions. These contrast agents may become a standard part of TRUS biopsy in the future.

Analysis of TRUS Images by Artificial Neural Networks

Another potential means of enhancing TRUS images and identifying malignant foci is the use of artificial neural networks. Automated image analysis, including pattern recognition and artificial neural networks (ANNs) applied to TRUS images, may successfully identify lesions that cannot be seen by the human eye. At present, such automated image analysis and pattern recognition are unavailable for existing TRUS systems.

ANNs, a type of artificial intelligence, are a software construct based roughly on the neural structure of the brain. Basic processing units called nodes simulate neurons, and weighted interconnections between the nodes simulate dendrites and axons.[48] The interconnection weights function as multipliers that simulate the connection strengths in the analogous biological model. The ANN is not programmed but learns by experience, via a "supervised learning" phase called training. Other types of ANNs may rely on an unsupervised learning method.[48] Cases that include inputs and known outputs, such as sets of clinical variables and a known pathological outcome, are presented to the ANN sequentially and repeatedly. A training algorithm automatically adjusts the connection weights, consequently changing the output values, to reduce errors between the actual ANN outputs and the expected outputs. As the ANN is trained, a set of connections is developed that allow for the largest number of correct predictions for the given training data set. The ANN is next validated with new cases not used previously. This "trained" ANN will function in a way similar to a mathematical function with inputs analogous to independent variables and outputs analogous to dependent variables. The ANN's performance can be measured by calculating the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for a specific ANN output cutoff. The overall performance (ie, over all output cutoffs) may be quantified by generating a receiver operator characteristic (ROC) curve.

In 1992, the first efforts to analyze TRUS images of the prostate were published.[49] ANN was able to distinguish between prostatic and nonprostatic tissues in TRUS images. Investigators have used ANNs for spectral analysis of ultrasound RF signals (pre-image) and ANNs to analyze ultrasound images of breast, colon, prostate, and other tissues, with promising results.[50,51] Workers at the University of Kiel, Germany, have assembled a prospective library of prostate tissue types by gathering TRUS images prior to radical prostatectomy (RP) and comparing these with whole-mount pathology slides.[52] In this work, an ANN was used to identify areas suspicious for cancer in a validation set of TRUS images. Preliminary data demonstrated that 99% of confirmed benign samples were correctly identified, with 79% of malignant lesions correctly classified. Ninety-seven percent of isoechoic cancers on TRUS were correctly classified by the ANN. Workers with the Artificial Neural Networks in Carcinoma of the Prostate (ANNs in CaP) Project (Crawford, Gamito, and associates) were able to confirm inde-

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pendently a subset of the results with the data of Loch and colleagues[52] by using an ANN to distinguish between Gleason grade 3 and 4 lesions. This model correctly identified 82% of grade 3 lesions and 67% of grade 4 lesions.

Crawford and colleagues from the Institute for Clinical Research in Washington, DC (ANNs in CaP Project) are developing software to analyze and interpret TRUS images through pattern recognition software, ANNs, and multivariate analysis. This technology will be developed to identify areas of TRUS images that are indicative of malignant lesions and to distinguish such areas from areas that show healthy tissue. TRUS images are to be gathered prior to RP at three study centers and correlated with the whole-mount prostate specimens. Using digital image processing software, TRUS image cross sections will be matched with their corresponding whole-mount sections, and areas of interest will be marked on the TRUS images. Image filters and pattern recognition software will be used to extract features/signatures from the TRUS images that will then be used to train an ANN. Software is also being developed to construct three-dimensional models from the TRUS cross sections. If these systems can identify malignant lesions within the prostate, a logical next step will be to develop a system to allow real-time direct biopsies of the prostate. This technology may also be applicable to other modalities such as magnetic resonance imaging (MRI) and CDI and may be used in future studies.[53,54]

The development of technologies to identify malignant lesions in TRUS images using a system of image filters, traditional statistical methods, and ANNs may have a positive impact on prostate cancer patients by improving the accuracy of needle biopsies. Furthermore, the ability to store three-dimensional images of the prostate may aid patients and their physicians in the watchful waiting strategy.

Repeat Needle Biopsy of the Prostate

Even though serum PSA is the most useful tumor marker for the diagnosis of patients with prostate cancer, this marker is still hampered by a lack of specificity. Until the enhanced ultrasound techniques such as contrast and ANNs become commonplace, many patients will require repeat prostate biopsy.

[Software] will be developed to identify areas of TRUS images that are indicative of malignant lesions and to distinguish such areas from areas that show healthy tissue.

Approximately two thirds of men undergoing prostate needle biopsy have benign histology. However, a 20% to 40% incidence of positive repeat biopsy in men with elevated PSA who had an initial negative biopsy has been demonstrated.[55] The presence of prostatic intraepithelial neoplasia or atypia on initial prostatic biopsy are predictive factors of high risk of invasive carcinoma and constitute an indication for repeat biopsy. Numerous studies have demonstrated that a significant number of men with an initial negative prostate needle biopsy but persistently elevated serum PSA level will have prostatic malignancy on subsequent biopsy. In a screening report by Catalona and colleagues[56] involving 9333 men in whom serial PSA measurements were taken, 25% of men with a PSA > 4.0 ng/mL undergoing a second, third, or fourth biopsy following an initial or repeated negative biopsy were found to have prostate cancer.

PSA exists in different molecular forms in the systemic circulation as free PSA, PSA bound to α_1-antichymotrypsin, and PSA bound to α_2-macroglobulin. The proportion of PSA α_1-anti-chymotrypsin was greater in patients with prostate cancer than in those with benign prostatic hyperplasia.[57,58] Subsequent studies were able to demonstrate some pattern of enhanced specificity without significantly sacrificing sensitivity. A recent multi-institutional trial revealed that patients with a free-to-total PSA ratio of ≤10% have a >50% probability of cancer.[59]

One approach toward identifying patients who could benefit from repeat biopsy is the use of the free-to-total PSA ratio as a predictor of prostate cancer. Brawer and colleagues[60,61] have studied archival specimens to determine the ability of the free-to-total ratio to predict subsequent prostate cancer. The median Hybritech free-to-total PSA ratio was significantly lower in patients with positive repeat prostate needle biopsy compared with those who had a negative biopsy (14.9% vs 19.4%, $P = .05$). Total PSA as well as the percent

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Table 4
Current Indications for Repeat Biopsy

- PSA > 10.0 ng/mL
- cPSA > 7.5 ng/mL
- cPSA/TPSA > 75%
- Strongly suspicious DRE
- Prostate volume > 60 cc

Dianon free-to-Hybritech total PSA ratio were not significantly different between the two groups of men.

For total PSA in the range of 2 to 15 ng/mL, the Hybritech free-to-total PSA ratio appeared to aid in the prediction of cancer on repeat biopsy A free-to-total PSA ratio in the range of 2 to 15 ng/mL as determined by Hybritech assay appeared to aid in the prediction of cancer on repeat biopsy when biopsy was previously negative. Although this study is limited by the relatively small sample size, the data suggest a potential use of the free-to-total PSA ratio to indicate a higher likelihood for the presence of missed clinically significant carcinoma; hence repeat prostate biopsy would be recommended in clinical practice and other settings. It should be noted that serial free-to-total PSA ratio measurements can be different among different assays; this should be considered when interpreting serial assays from different labs.[60,61]

To define the role of repeat needle biopsy further, Brawer and colleagues[62] presented data on 100 sextant prostate needle biopsies without a diagnosis of malignancy, which were repeated. Carcinoma was detected in 20 repeat biopsies (20%). Stratification based on initial biopsy result revealed carcinoma in 10 of 69 cases (14.5%) without prostatic intraepithelial neoplasia or atypia, 5 of 17 (29.4%) with atypia, 5 of 5 (100%) with grade II or III prostatic intraepithelial neoplasia, and 0 of 9 with grade I prostatic intraepithelial neoplasia. PSA and PSA velocity did not provide statistically significant stratification, perhaps because of the wide variance in these parameters and the small sample size.

These results suggest that patients with a diagnosis of glandular atypia, or grade II or III prostatic intraepithelial neoplasia on initial biopsy, are at high risk for invasive carcinoma and should undergo repeat prostate needle biopsy.[62] A rapidly increasing serum PSA level or grossly abnormal digital rectal examination may also indicate carcinoma not discovered on initial biopsy (see Table 4).[63]

Conclusions

Advances continue in the area of early diagnosis of prostate cancer. With the advent of PSA-based screening in the early 1990s, we are witnessing a slow and steady decline in the death rates from prostate cancer. The new tools and approaches reviewed here will continue to fuel improvements in the outcome of patients with prostate cancer. ■

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Main Points

- Every attempt should be made to detect prostate cancer early, for successful treatment.
- The identification of genetic abnormalities in prostate cancer will allow screening for early disease; some possible gene loci have already been determined.
- Prostate cancer risks include race, family history, and perhaps certain serum markers such as insulin-like growth factor I.
- Transrectal ultrasound (TRUS)-guided biopsy has become the standard for diagnosis.
- Artificial neural networks (ANNs), pattern recognition, and certain contrast agents, all in combination with TRUS, are being explored in order to improve diagnostic accuracy.
- New criteria for follow-up biopsy after an initial negative biopsy are being developed. These include the free-to-total PSA ratio as well as any abnormalities seen on the initial biopsy, such as atypia or high-grade prostatic intraepithelial neoplasia.

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